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Subchronic Toxicity of Tetrachloroethylene (Perchloroethylene) Administered in the Drinking Water of Rats

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16. ABSTRACT

Tetrachloroethylene (perchloroethylene) has been identified in drinking water at a concentration of approximately 1 ug/liter and in ambient air at levels of 0.18-4.5 ppb (0.0012-0.03 mg/m^3). Much of the available toxicological data are from inhalation or gavage studies. This study provides data on the effects of tetrachloroethylene in drinking solutions. The acute oral LD_{50} was determined in male and female Charles River rats and found to be 3835 mg/kg for males and 3005 mg/kg for females. Male and female rats received theoretical daily doses of 14, 400 and 1400 mg tetrachloroethylene/kg bw/day for 90 consecutive days. There were no compound related deaths. Body weights were significantly lower in male and female rats at the higher doses. There were no consistent dose related effects on any of the hematological or urinalysis parameters. 5'Nucleotidase activity was increased in a dose dependent manner, suggesting possible hepatotoxicity; other blood chemistry parameters were unaffected by the treatment. There were no gross pathological effects observed. Liver and kidney ratios were elevated at the higher doses. There was no apparent evidence of accumulation. These data suggest that exposure of humans to reported levels of tetrachloroethylene in drinking water does not constitute a serious health hazard.

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The Subchronic Toxicity of Tetrachloroethylene (Perchloroethylene) Administered in the Drinking Water of Rats[1,2]

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The Subchronic Toxicity of Tetrachloroethylene (Perchloroethylene) Administered in the Drinking Water of Rats. HAYES, J. R., CONDIE, L. W., JR., AND BORZELLECA, J. F. (1986). *Fundam. Appl. Toxicol.* 7, 119–125. This study provides data on the effects of tetrachloroethylene in drinking solutions. The acute oral LD50 in male and female Charles River rats was found to be 3835 mg/kg for males and 3005 mg/kg for females. Male and female rats received theoretical daily doses of 14, 400, and 1400 mg tetrachloroethylene/kg body wt/day for 90 consecutive days. There were no compound-related deaths. Body weights were significantly lower in male and female rats at the higher doses. There were no consistent dose-related effects on any of the hematological, clinical chemistry, or urinalysis parameters. 5'-Nucleotidase activity was increased in a dose-dependent manner, suggesting possible hepatotoxicity; however, other serum indicators of hepatic function were unaffected by the treatment. There were no gross pathological effects observed. Liver and kidney body weight ratios, but not brain weight ratios, were elevated at the higher doses. There was no other evidence of compound-related toxicity. These data suggest that exposure of humans to reported levels of tetrachloroethylene in drinking water (approximately 1 μg/liter) does not constitute a serious health hazard. © 1986 Society of Toxicology.

Tetrachloroethylene (perchloroethylene (PERC); 1,1,2,2-tetrachloroethylene; $CCl_2 = CCl_2$; CASRN:127-18-4) has the following properties: mol. wt. is 165.85; it is a colorless liquid; sp grav. is 1.624; it is relatively insoluble in water (150 mg/liter); at standard temperature and pressure 1 ppm is equivalent to 6.78 mg/m^3; it has negligible photochemical reactivity; and in contact with water, PERC decomposes to trichloroacetic and hydrochloric acids (USEPA, 1985).

Some of the principal uses of tetrachloroethylene include: solvent in dry cleaning, degreasing agent, fumigant for dried vegetables, cleaner for rugs and upholstery, paint and stain remover, and an intermediate in the production of organic compounds. Approximately 265,000 metric tons of tetrachloroethylene were produced in the United States in 1982 (USEPA, 1985). Tetrachloroethylene is relatively stable in the environment. Average ambient air concentrations "range from trace amounts in rural areas to as much as 10 parts per billion (ppb) or 0.068 mg/m^3 in some large urban centers" (USEPA, 1985). It has been detected in rain water (0.15 μg/liter), surface waters (0.12–0.26 μg/liter), and in tap water (as high as 82.5 μg/liter) (Giger and Molnar-Kubica, 1978; Wakeham *et al.*, 1980). The water supply for a number of cities may contain approximately 1–2 μg/liter (ppb) (USEPA, 1985).

The available toxicological data have been critically reviewed for the USEPA (1985) and will be highlighted only. Toxicological effects of PERC in humans after oral, inhalation, and

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[2] This paper has not been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies, and therefore its contents do not necessarily reflect the view of the Agency and no official endorsement should be inferred.

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skin contact include: central nervous system (CNS) depression (weakness, ataxia, restlessness), cardiac and respiratory depression, depressed liver and kidney function, irritation of eyes and skin, and altered immune responses (Reichert, 1983; USEPA, 1985). Animal studies have revealed the following as target organs: nervous system, liver, kidney, and possibly the immune system.

The potential genotoxicity of PERC has been evaluated in a number of systems. Positive responses were observed in some systems only at cytotoxic concentrations (USEPA, 1985). PERC did not form adducts with DNA (Schumann *et al.*, 1980). The lack of consistent, dose-dependent genotoxicity contrasts with that of several other chlorinated ethylenes such as vinyl chloride and trichloroethylene. This is partly due to the lower chemical reactivity of the oxiranes metabolically produced from chlorinated ethylenes with symmetrical distribution of the chlorine atoms when compared with the reactivity of oxiranes from ethylenes with asymmetric chlorines (Henschler and Bonse, 1977; Jones and Mackrodt, 1982).

PERC appears to be a suspect animal carcinogen. A gavage bioassay resulted in a significant incidence of hepatocellular carcinomas in male and female mice, but the results in rats were inconclusive due to excess mortality (NCI, 1977). Rampy *et al.* (1977) reported no increase in tumor incidence in rats exposed to PERC by inhalation.

Schwetz *et al.* (1975) exposed Swiss Webster mice and Sprague–Dawley rats to PERC at levels up to 300 ppm, 7 hr/day, on Days 6–15 of gestation. No evidence of teratogenicity was reported. Beliles *et al.* (1980) also exposed Sprague–Dawley rats to PERC at levels up to 300 ppm, 7 hr/day, 5 days/week for 3 weeks prior to mating and between Days 0 and 18 or 6 and 18 of gestation. No teratogenic effects were noted. However, Tepe *et al.* (1982) exposed Long–Evans hooded rats to 1000 ppm PERC 6 hr/day, 5 days/week for 2 weeks before mating and/or during gestation. Embryotoxic effects and soft tissue variations were noted in rats exposed only during gestation. Excessive skeletal variations were observed in rats exposed before mating and during gestation. Beliles *et al.* (1980) exposed New Zealand rabbits to 500 ppm PERC, 7 hr/day, 5 days/week for 3 weeks prior to gestation and/or during Days 0–21 of gestation. No teratogenic effects were observed.

PERC is absorbed through the lungs, gastrointestinal tract, and skin (e.g., Tsuruta, 1975). Its major route of excretion is via the lung (unmetabolized) followed by urine and feces (Pegg *et al.*, 1979; Frantz and Watanabe, 1983; Reichert, 1983). Pharmacokinetic data indicate that PERC can accumulate in the fat due to its lipid solubility and slow metabolism (Filser and Bolt, 1979). Schumann *et al.* (1980) also studied the pharmacokinetics of PERC in mice and rats as it relates to oncogenicity and reported that the mouse metabolizes PERC faster than the rat. PERC is metabolized to its oxirane (Leibman and Ortiz, 1977; Schumann *et al.*, 1980) which rearranges to trichloroacetylchloride which then hydrolyzes to trichloroacetic acid (Henschler and Hoos, 1982). Ikeda (1977) reported on the metabolism of PERC in humans; trichloroethanol and trichloroacetic acid are the metabolites and the mean urinary half-life for PERC is 144 hr.

There are a limited number of studies of the potential adverse health effects of tetrachloroethylene in drinking water. For example, Utzinger and Schlatter (1977) reviewed the toxicity of trace amounts of PERC in drinking water and concluded that "the daily uptake of 50 mg Cl_2C: CCl_2 by humans either by the oral or by the respiratory route can be considered acceptable." Frantz and Watanabe (1983) exposed male Sprague–Dawley rats to saturated water solutions of PERC (150 ppm = 8.1 ± 3.1 mg/kg/day) for 12 hr. They concluded that the fate of PERC following exposure in drinking water is not significantly different from gavage or inhalation exposure.

The following studies were conducted with the cooperation of the USEPA to provide data on the acute and subchronic toxicity of PERC administered in drinking water since there is an apparent paucity of such data.

METHODS

Tetrachloroethylene

Tetrachloroethylene (Lot 1019KJ) was obtained from Aldrich Chemical Company (Milwaukee, Wisc.). Gold label, spectrophotometric grade tetrachloroethylene with a purity of 99+% was employed throughout the studies. Tetrachloroethylene was administered via drinking water solutions. These were prepared twice weekly by the addition of tetrachloroethylene to 4% Emulphor[4] (a polyoxyethylated vegetable oil, GAF Corp., Linden, N.J.) in deionized water. Vigorous, rapid stirring for several hours was necessary to ensure homogeneity. The solution was pumped into glass water bottles with cork stoppers and stainless-steel sipper tubes with ball bearings to minimize leakage. Naive controls received deionized water; vehicle controls received 4% Emulphor in deionized water.

Animals and Maintenance

Male and female Sprague–Dawley-derived CD rats, 22–30 days of age, were obtained from Charles River Breeding Laboratories (Wilmington, Mass.). Rats were computer randomized, caged individually, and quarantined for 1 week prior to initiation of the studies. They were maintained in stainless-steel wire-bottomed suspended cages, color coded for dosage level, in a temperature-controlled animal room at 21–24°C with a relative humidity of 40–60%. A 12-hr light–dark cycle was maintained. For the subchronic study, the cages were distributed in each rack so that each dosage level was equally represented at the various positions, thereby minimizing differences among the groups due to light, temperature, and air flow. Purina Rodent Chow 5001 (Ralston Purina Co., St. Louis, Mo.) and drinking solutions were available *ad libitum*.

Acute Toxicity

Male and female rats, weighing 165–208 g and 120–175 g, respectively, were divided into eight dosage groups consisting of five rats per sex per group. Animals were dosed by stomach tube following an overnight fast (16 hr). The volume administered was 10 ml/kg body wt. The dose ranges utilized were 2200–8850 mg/kg for the males and 2200–5500 mg/kg for the females. Doses were based upon initial range-finding studies. Hourly observations were made during the first 9 hr after administration of tetrachloroethylene followed by twice-daily observations for the next 14 days. All animals that died during the 14-day observation period and all survivors were necropsied.

Subchronic Toxicity

For these studies, the rats were divided into five groups consisting of 20 males and 20 females per group. The groups were (1) naive untreated (naive control); (2) 4% Emulphor vehicle (vehicle control); (3) 14 mg PERC/kg; (4) 400 mg PERC/kg; and (5) 1400 mg PERC/kg. Water bottles were changed on Mondays and Thursdays between the hours of 8:00 AM and 12:00 noon. The exposure period was 90 consecutive days.

Parameters monitored. The rats were observed twice daily (at least 5 hr apart) for general appearance, signs of intoxication, and mortality. Animals found either moribund or dead were immediately necropsied. Body weights were recorded on the first day of exposure, weekly thereafter on the same day and at approximately the same time, and at sacrifice. Consumption of drinking solutions was determined twice weekly.

Hematology and serum chemistry determinations were conducted at the end of the 90-day exposure period on 10 males and 10 females randomly selected from each group for each type of study. Hematologic parameters evaluated included: hemoglobin (as cyanmethemoglobin); hematocrit (microhematocrit); erythrocytes, leukocytes, and platelets (Coulter counter, Model Z81); differentials (Wright–Giemsa stain); fibrinogen and prothrombin times (Dade Diagnostics Reagents). Blood chemistry determinations were conducted with an Abbott bichromatic analyzer and diagnostic kits from Abbott Labs and Sigma Chemical. Ion concentrations were determined with a flame photometer and a chloridometer. Serum was analyzed for LDH, SGPT, SGOT, ALP, 5'-nucleotidase, BUN, protein, glucose, cholesterol, bilirubin, creatinine, calcium, phosphorus, albumin, globulin, sodium, potassium, and chloride. Urinalyses of all animals were performed with Labstix regeant strips (Miles Laboratories, Inc.) Urine was analyzed for pH, bilirubin, glucose, protein, ketones, and occult blood.

Necropsy. The rats were weighed and anesthetized with ether and blood was collected by cardiac puncture into 3.0% sodium citrate (1:10 citrate:blood) for the hematology studies and into uncitrated tubes for the serum chemistries. Gross pathological examination was performed, followed by the removal and weighing of selected organs. All tissues were preserved in 10% neutral buffered Formalin.

Statistical considerations. The LD50 was determined by the method of Litchfield and Wilcoxon (1949). All subchronic data were subjected to an analysis of variance and Dunnett's *t* test; nonhomogeneous data were subjected to a Wilcoxon rank sum test. Those values which differed from the vehicle control group at $p \leq 0.05$ were considered statistically significant.

[4] Emulphor has been used in previously reported drinking water studies (acute and subchronic) from this laboratory. There is no evidence that Emulphor has an adverse effect on any of the many parameters measured.

RESULTS

Acute Toxicity

The LD50 and confidence limits for male and female rats were 3835 (3318–4437) and 3005 (2689–3358) mg/kg, respectively. All deaths occurred within the first 24 hr with a trend toward decreasing time to death with increasing dosage.

Tremors were observed at all doses. Tremors, ataxia, and central nervous system depression preceded death. Gross necropsy findings of the rats that died were essentially negative; hemorrhagic lungs and adrenals were observed in some animals.

No gross pathology was observed in the animals that survived the 14-day postadministration observation period.

Subchronic Toxicity

Fluid consumption. Fluid consumption is shown in Figs. 1 and 2. Daily fluid consumption decreased during the course of the study. There is no explanation for this phenomenon.

Body weights. Mean body weight data are summarized in Figs. 3 and 4. Significantly lower body weights were observed in males receiving 1400 mg/kg and in females receiving 400 or 1400 mg/kg/day.

Hematology. No consistent compound-related effects were observed in any of the parameters measured.

Serum chemistry. There were no consistent compound-related effects in any of the parameters measured except with 5′-nucleotidase which was significantly elevated in females at the highest dose and in males at the two higher doses (400 and 1400 mg/kg/day).

Urinalysis. There were no significant consistent dose-related or compound-related effects.

Mortality. There were no compound-related deaths in either males or females. No gross pathology was observed in animals that died during the treatment period (three male naive controls; three females at 400 mg/kg and one female at 1400 mg/kg).

Organ weights and ratios. Liver and kidney to body weight ratios were higher in males and females at the highest dose; the kidney ratio was also higher in males at the mid dose. However, the liver and kidney to brain weight ratios were not significantly different from the vehicle control. The brain weight but not the

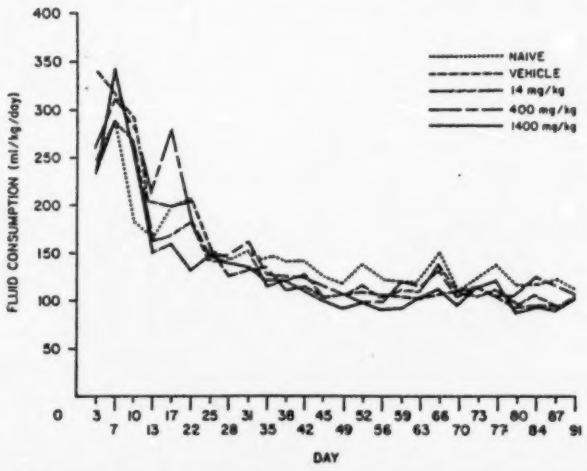

FIG. 1. Fluid consumption for male CD rats exposed to tetrachloroethylene for 91 days.

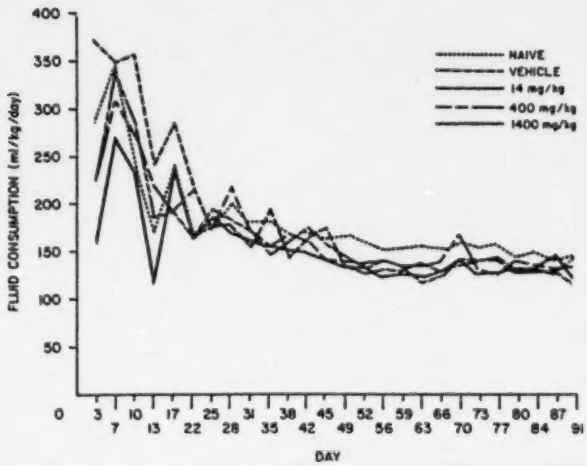

FIG. 2. Fluid consumption for female CD rats exposed to tetrachloroethylene for 91 days.

brain to body weight ratio was lower in females receiving the highest dose.

DISCUSSION

The toxicity of tetrachloroethylene has been extensively and critically reviewed (USEPA, 1985). There exists a considerable body of data based on inhalation but very little data on oral ingestion (in food or water). There are a limited number of gavage studies but only one study was identified in which PERC was administered in drinking water. Utzinger and Schlatter (1977) reviewed the toxicity of trace amounts of tetrachloroethylene in water and concluded that the daily uptake of 50 mg

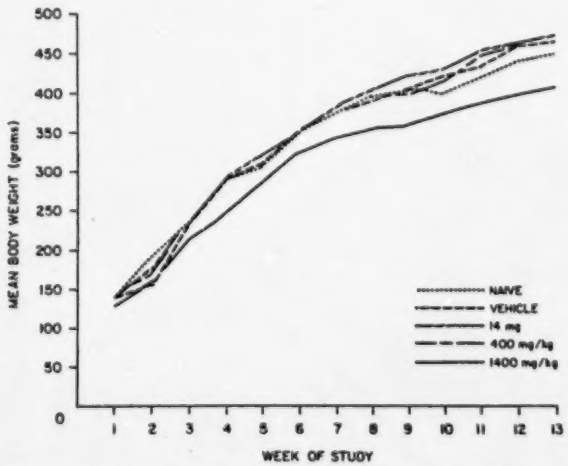

FIG. 3. Weekly mean body weights of male CD rats exposed to tetrachloroethylene for 13 weeks.

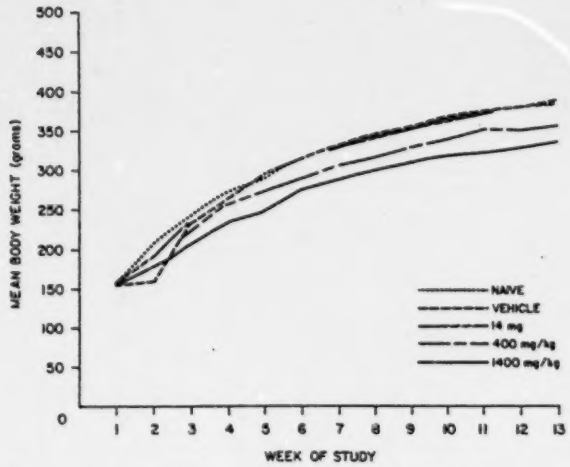

FIG. 4. Weekly mean body weights of female CD rats exposed to tetrachlorothylene for 13 weeks.

PERC by either the oral or the respiratory route by humans can be considered acceptable.

In the studies reported herein, the primary effect of ingested PERC was on body weight gain. This effect was apparently not due to decreased food or fluid consumption. There was no evidence of diarrhea. Liver and kidney to body weight ratios were increased in a dose-dependent fashion. However, the liver and kidney to brain weight ratios were not statistically different. This is a more meaningful ratio since it minimizes the effect of body weight changes. These two organs could be target organs but there are no biochemical (serum) data to support this. For example, the increase in activity of 5'-nucleotidase would suggest cholestasis. However, other serum chemistries do not support the hepatoxicity (or nephrotoxicity) of ingested tetrachloroethylene at these dose levels. Gross examination of tissues failed to reveal any abnormalities.

The doses used in the NCI bioassay (NCI, 1977) were 941 and 471 for male rats and 949 and 474 for female rats. The PERC was dissolved in corn oil and administered by gavage. There was a lower weight gain among the treated rats. Other effects reported were probably due to the presence of pneumonia (≥62% of rats in each group). The kinetics following bolus administration in corn oil are probably significantly different from administration in emulphor:water solution. A significant comparison of the two studies is therefore precluded.

The data presented appear to confirm the conclusions of Utzinger and Schlatter (1977), and the USEPA (1985) that exposure of humans to environmental levels of PERC (air, water) does not constitute a serious health hazard.

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